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PATENT SPECIFICATION

DRAWINGS ATTACHED

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COMPLETE SPECIFICATION

Process for the Preparation of Sustained Action Tablets

We, COLLETT & Co. A/S of Vitaminveien 11, Oslo, Norway, a Norwegian Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described, in and by the following statement:—

The present invention relates to the preparation of a mass which may be formed into tablets or other embodiments, or transformed into granules and compressed to tablets, whose contents of soluble, therapeutically active substances are released slowly into the gastric and intestinal juices.

Several processes for the production of sustained action tablets are known. These processes are usually effected by coating the soluble active substances with slightly soluble substances which slowly dissolve in the gastric and intestinal juices and thereby release the active substances. The active substances may also be contained in solid particles having an inner core having a coating of slightly soluble substance, a coating of soluble active substance over this, and an outer slightly soluble coating so that the active substance is released from the tablet in portions.

However, these processes are inconvenient and expensive and there are technical difficulties envolved in obtaining the desired properties. A process is also known where the soluble, active substance in powder form with or without a water soluble carrier substance, is mixed with a slightly soluble substance e.g. plastic, also in powder form, and this mixed powder is then compressed to a tablet. The soluble, active substance is released from this tablet in the gastric juices, and the slightly soluble substance remains as a skeleton or a porous tablet. The rate of release of active substance depends upon conditions such as compression pressure.

The advantages obtained by sustained action tablets or tablets which release their active substances according to a controlled programme, are generally recognised and the tablets are used, even though there are no production methods capable of giving results without one or more series defects in the finished product. Examples of typical defects are pH dependence, great variations in the rate of dissolution, expensive and difficult production technique, change in the solubility during storage of the preparation, dependence of the retardation on the degree of compression of the tablets and the possibility of oxidation of the active substances.

The present invention consists in a process for the preparation of sustained action pharmacuetical tablets comprising emulsifying a warm, molten sugar mass having a 1—4% water content with a non-toxic, thermoplastic substance substantially insoluble in gastric or intestinal juices, the proportions of thermoplastic substance to sugar mass being such as to form an emulsion in which the thermoplastic substance forms the continuous phase, cooling the emulsion until it solidifies and forming the solidified dispersion obtained into tablets, the therapeutically active ingredients of the tablets being either incorporated into the water soluble phase of the emulsion or intimately mixed with the solidified dispersion.

Preferably, the sugar mass comprises a mixture of mono-and disaccharides.

The tablet obtained may be described as a continuous matrix of thermoplastic material enclosing the discrete particles of sugar and therapeutically active ingredients. Upon ingestion, the soluble sugar mass and therapeutically active ingredients dissolve in contact with gastric or intestinal juices and the thermoplastic, substantially insoluble substance re-

mains as a porous skeleton. The thermoplastic substance should comprise at least 10% by weight of the total mass.

The thickness of the enclosing, substantially insoluble matrix depends on the ratio of the components used and this also effects the rate at which the soluble sugar mass and active ingredients diffuse through the matrix when brought into contact with the gastric or intestinal juices.

A further advantage in the tablets produced according to this invention is the continuous release of all the active substance present in the tablets. The basic material contains water soluble carbohydrates and water insoluble resins in a solid emulsion which allows the water to penetrate the tablets and release all water soluble substances. There is no risk of the active substance remaining enclosed and inaccessible within the water-insoluble substance, as may happen in the mixtures of active substance and plastic in powder form.

A further advantage of the fact that the mass contains easily soluble carbohydrates, is that the stability of the active substance is ensured and the mass is prevented from hardening during storage, which leads to an increasingly slower rate of solubility.

In practice, any non-poisonous thermoplastic substance may be used if it is substantially insoluble in gastric juices, and become liquid on heating so that it may be emulsified with warm sugar. Examples of such substances, are natural rubbers, such as chicle gum and latex, and synthetic elastomers such as cis- and transpolybutadiene and polyisobutylene. Such materials are sometimes referred to as "Chewing Gum Base" and a list of such substances which have been found to be particularly suitable is given under the heading of "Chewing Gum Base" in the U.S. Federal Register for September 23, 1961.

The invention will be further described with reference to the following examples.

EXAMPLE 1.

The soluble portion of the mass is prepared by melting a mixture of sugars, the mixture depending on the desired melting temperature of the finished product. However, a suitable mixture is 46% sucrose, 16% invert sugar and 38% glucose syrup.

This mixture is heated, preferably under vacuum, until a mass with a water content of 1—4% is obtained.

This mass is mixed in melted, warm condition with a suitable thermoplastic, natural or synthetic elastomer such as "chicle gum". A suitable percentage of sugar and gum is 20% chicle gum and 80% sugar mass. After the two masses are completely mixed or emulsified the whole is cooled to a solidified dispersion, which may be reduced to granules of desired size and further compressed into tablets.

As an alternative, the subdivision of the mass may be undertaken while it is still warm, e.g. by pressing in a die or rolling between engraved rollers. By suitable shaping of the subdivided pieces the mass may, in this way, be directly transformed into tablets having retarded solubility as described.

The active substances to be contained in the tablets are mixed in the warm carbohydrate mass either before or during emulsification with the thermoplastic substance, the active substances being distributed homogeneously through the mixture by stirring. In another embodiment the active substances are mixed with the granules prepared as described above in a dry state and the compression to tablets is carried out in the normal manner, after which the tablets are preferably sintered in a manner known per se, e.g. by heating to 55°C, so that the tablet becomes compact and coherent. In the sintering process the interfaces between the granule particles will be eliminated, the mass will become homogeneous and the active particles embedded in the mass so that the desired retarded solubility effect is obtained.

In the following table examples are given of the composition of tablets produced according to the present invention.

TABLE

Tablet weight	600 mg	500 mg	400 mg
Sugar mass	64%	52%	56%
"Chicle gum" or the like	20%	28%	40%
Ascorbic acid	16%	—	—
Riboflavin	—	20%	—
D-Amphetamine sulphate	—	—	4%

The invention will be further described with reference to the accompanying drawings in which:—

Fig. 1 shows solubility curves illustrating that the release of active substances from the tablets is insignificantly dependent on the pH-value of the environment. The vertical axis indicated the amount of active substances released into the solution expressed as per cent total content in the tablet. It will be seen that the rate of release is greatest at the beginning, which means that the desired concentration in the blood is obtained relatively rapidly, and that the subsequent progress of

the curve may be regarded as approximately linear, which means that the amount released per time unit is approximately constant over a longer period.

Fig. 2 shows solubility curves for active substances from tablets examined by means of the method described as "Tablet disintegration test" in the U.S. pharmacopoeia XVI with the following modifications: The apparatus is filled with artificial gastric juice with a pH-value of 1.8, and, after 1 hour, half of the volume is replaced by artificial intestinal juice with a pH-value of 7.6. After another hour, half of the volume is again replaced by artificial intestinal juice, and so on, every hour in a corresponding manner. The quantity of active substance dissolved is determined, either in the fluid volume withdrawn, or from analysis of tablets which are taken from the apparatus at hourly intervals.

The percentage figures in fig. 2 give the tablets' content of chicle gum or similar elastomers. It is apparent from the curves that the rate of release of active substances may be regulated by varying the percentage of thermoplastic substance.

By the method described it is also possible to prepare tablets containing a mixture of constituents containing different therapeutically active substances, e.g. substances which are not normally stable when admixed with one another, but which may be incorporated in the same tablet when the substances are stirred into individual base sugar masses, as previously described, and which will be released *in vivo* at the desired rate.

An alternative method of preparing the tablets containing granules having different therapeutically active substances is to compress the different granules in layers, without mixing, according to generally known technique so as to obtain tablets consisting of several layers. This allows the possibility of further control of the rate of release of the active substances, since this rate will be determined for each tablet layer by the ratio between the water soluble phase and thermoplastic substance. The tablets are sintered by heating to a temperature at which the interior of the tablets becomes compact and coherent whereby a preparation is obtained which in the "Tablet Disintigration Test" gives a reproducible release curve of active ingredients, independent of variations in the compression pressure in the tablet forming machine.

WHAT WE CLAIM IS:—

1. A process for the preparation of sustained action pharmaceutical tablets comprising emulsifying a warm, molten sugar mass having a 1—4% water content with a non-toxic, thermoplastic substance substantially insoluble in gastric or intestinal juices, the proportions of thermoplastic substance to sugar mass being such as to form an emulsion in which the thermoplastic substance forms the continuous phase, cooling the emulsion until it solidifies and forming the solidified dispersion obtained into tablets, the therapeutically active ingredients of the tablets being either incorporated into the water soluble phase of the emulsion or intimately mixed with the solidified dispersion.

2. A process as claimed in claim 1 wherein the sugar mass comprises a mixture of mono- and disaccharides.

3. A process as claimed in claim 1 or 2 wherein the solidified dispersion is reduced to granules which are then compressed into tablets.

4. A process as claimed in claim 3 wherein the thermapeutically active ingredients of the tablets are intimately mixed with the granules which are then compressed into tablets and sintered by heating to a temperature at which the tablet becomes compact and coherent.

5. A process as claimed in claim 4 in which the tablets are sintered by heating them to 55°C.

6. A process as claimed in any preceding claim wherein the thermoplastic substance comprises at least 10% by weight of the total mass.

7. A process as claimed in any of claims 1 to 3 wherein the therapeutically active ingredients of the tablets are added to the warm, molten sugar mass before emulsification with the thermoplastic substance.

8. A process as claimed in any of claims 1 to 3 wherein the therapeutically active ingredients of the tablets are added to the warm emulsion of sugar mass and thermoplastic substance.

9. A process as claimed in any preceding claim wherein the non-toxic thermoplastic substance is selected from natural rubbers and synthetic elastomers.

10. A process as claimed in claim 9 wherein the natural rubber is chicle gum of latex.

11. A process as claimed in claim 9 wherein the synthetic elastomer is cis- or trans-polybutadiene or polyisobutylene.

12. A process as claimed in claim 3 wherein the tablets are formed from granules containing different therapeutically active ingredients.

13. A process for the preparation of sustained action tablets substantially as hereinbefore described with reference to any one of the Examples given.

14. Sustained action tablets when prepared by the process claimed in any preceding claim.

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1 SHEET *This drawing is a reproduction of the Original on a reduced scale*

FIG.1

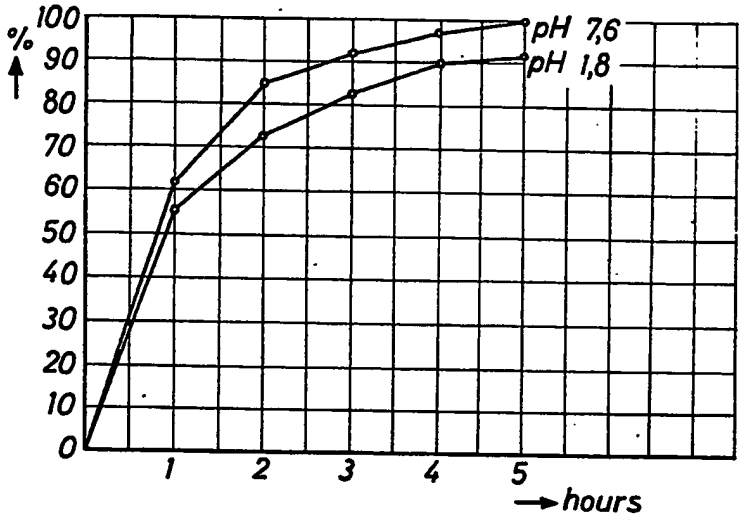

FIG.2